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**Patentanmeldung Nr. Patent application No. Demande de brevet n°**

99103723.5

**PRIORITY DOCUMENT**
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Der Präsident des Europäischen Patentamts:
Im Auftrag

For the President of the European Patent Office

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# Blatt 2 der Bescheinigung
# Sheet 2 of the certificate
# Page 2 de l'attestation

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Titre de l'invention:
Use of substituted 4-biarylbutyric and 5-biarylpentanoic acid derivatives for the treatment of cerebral diseases

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# Use of Substituted 4-Biarylbutyric and 5-Biarylpentanoic Acid Derivatives for the Treatment of Cerebral Diseases



## Field

This invention relates to the use of enzyme inhibitors, and more particularly, to known matrix metalloprotease-inhibiting 4-Biarylbutyric Acids and 5-Biarylpentanoic Acids and derivatives thereof, for the prevention and treatment of cerebral diseases.

## Background

Substituted 4-Biarylbutyric and 5-Biarylpentanoic Acid Derivatives as Matrix Metalloprotease Inhibitors are described in WO 96/15096, WO 97/43237, WO 97/43238, WO 97/43239, WO 97/43240, WO 97/43245, WO97/43247 and WO 98/22436.

The matrix metalloproteases (matrix metalloendo-proteinases or MMPs) are a family of zinc endoproteinases which include, but are not limited to, interstitial collagenase (MMP-1), stromelysin (proteoglycanase, transin, or MMP-3), gelatinase A (72kDa-gelatinase or MMP-2), neutrophil collagenase (MMP-8), gelatinase B (95kDa-gelatinase or MMP-9) and macrophage elastase (MMP-12). These MMPs are secreted by a variety of cells including fibroblasts, chondrocytes, granulocytes and macrophages along with natural proteinatious inhibitors known as TIMPs (Tissue Inhibitor of MetalloProteinase).

All of these MMPs are capable of destroying a variety of connective tissue components of articular cartilage or basement membranes and a wide variety of extracellular matrix proteins. Each MMP is secreted as an inactive proenzyme which must be cleaved in a subsequent step before it is able to exert its own proteolytic activity. In addition to the matrix destroying effect, certain of these MMPs such as MMP-3 have been implemented as the *in vivo* activator for other MMPs such as MMP-1 and

MMP-9 (A. Ho, H. Nagase, Arch. Biochem. Biophys., 267, 211-16 (1988); Y. Ogata, J.J. Enghild, H. Nagase, J. Biol. Chem., 267, 3581-84 (1992)). Thus, a cascade of proteolytic activity can be initiated by an excess of MMP-3. It follows that specific MMP-3 inhibitors should limit the activity of other MMPs that are not directly inhibited by such inhibitors.

MMP inhibitors may also be useful in the inhibition of other mammalian metalloproteases such as the adamalysin family (or ADAMs) whose members include TNFα converting enzyme (TACE) and ADAM-10, which can cause the release of TNF from cells.

**Summary**

This invention relates to the use for the prevention and treatment of cerebral diseases of compounds having matrix metallprotease inhibitory activity of the generalized formula (I) :

$$(T)_xA\text{-}B\text{-}D\text{-}E\text{-}CO_2H\ . \qquad (I)$$

In the above generalized formula (I), $(T)_xA$ represents a substituted or unsubstituted aromatic 6-membered ring or heteroaromatic 5 - 6 membered ring containing 1 - 2 atoms of N, O, or S. T represents one or more substituent groups, the subscript x represents the number of such substituent groups, and A represents the aromatic or heteroaromatic ring, designated as the A ring or A unit. When N is employed in conjunction with either S or O in the A ring, these heteroatoms are separated by at least one carbon atom.

The substituent group(s) T are independently selected from the group consisting of halogen; alkyl; haloalkyl; haloalkoxy; alkenyl; alkynyl; $-(CH_2)_pQ$ in which p is 0 or an integer of 1 - 4; -alkenyl-Q in which the alkenyl moiety comprises 2 - 4 carbons; and alkynyl-Q in which the alkynyl moiety comprises 2 - 7 carbons. Q in the latter three groups is selected from the group consisting of aryl, heteroaryl, -CN, -CHO,

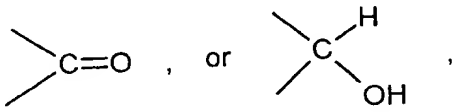
$-NO_2$, $-CO_2R^2$, $-OCOR^2$, $-SOR^3$, $-SO_2R^3$, $-CON(R^4)_2$, $-SO_2N(R^4)_2$, $-COR^2$, $-N(R^4)_2$, $-N(R^2)COR^2$, $-N(R^2)CO_2R^3$, $-N(R^2)CON(R^4)_2$, $-CHN_4$, $-OR^4$, and $-SR^4$.

In these formulae $R^2$ represents H, alkyl, aryl, heteroaryl, arylalkyl, or heteroaryl-alkyl. $R^3$ represents alkyl, aryl, heteroaryl, arylalkyl, or heteroaryl-alkyl. $R^4$ represents H; alkyl; aryl; heteroaryl; arylalkyl; heteroaryl-alkyl; alkenyl; alkynyl; alkyleneoxy, polyalkyleneoxy, alkylenethio or alkyleneamino terminated with H, alkyl, or phenyl; haloalkyl; lower alkoxycarbonyl; or acyl. When two $R^4$ groups are situated on a nitrogen, they may be joined by a bond to form a heterocycle, such as, for example, a morpholine, thiomorpholine, pyrrolidine, or piperidine ring.

Unsaturation in a moiety which is attached to Q or which is part of Q is separated from any N, O, or S of Q by at least one carbon atom. The A ring may be unsubstituted or may carry up to 2 substituents T. Accordingly, the subscript x is 0, 1, or 2.

In the generalized formula (I), B represents a bond or an optionally substituted aromatic 6-membered ring or a heteroaromatic 5 - 6 membered ring containing 1 - 2 atoms of N, O, or S. When B is a ring, it is referred to as the B ring or B unit. When N is employed in conjunction with either S or O in the B ring, these heteroatoms are separated by at least one carbon atom. There may be 0 -2 substituents T on ring B.

In the generalized formula (I), D represents




in which $R^2$ is defined as above and each $R^2$ may be the same or different.

In the generalized formula (I), E represents a chain of n carbon atoms bearing m substituents $R^6$, in which the $R^6$ groups are independent substituents, or constitute spiro or nonspiro rings. Rings may be formed in two ways: a) two groups $R^6$ are joined, and taken together with the chain atom(s) to which the two R6 group(s) are attached, and any intervening chain atoms, constitute a 3 - 7 membered ring, or b) one group $R^6$ is joined to the chain on which this one group $R^6$ resides, and taken together with the chain atom(s) to which the $R^6$ group is attached, and any intervening chain atoms, constitutes a 3 - 7 membered ring. The number n of carbon atoms in the chain is 2 to 4, and the number m of $R^6$ substituents is an integer of 1 - 3.

Each group $R^6$ is independently selected from the group consisting of:

*fluorine;

*hydroxyl, with the proviso that a single carbon atom may bear no more than one hydroxyl group;

*alkyl;

*aryl;

*heteroaryl;

*arylalkyl;

*heteroaryl-alkyl;

*alkenyl;

*aryl-substituted alkenyl;

*heteraryl-substituted alkenyl;

*alkynyl;

*aryl-substituted alkynyl;

*heteroaryl-substituted alkynyl;

*$-(CH_2)_tR^7$, wherein t is 0 or an integer of 1 - 5 and

$R^7$ is selected from the group consisting of:

*N-phthalimidoyl;

*N-(1,2-naphthalenedicarboximidoyl);

*N-(2,3-naphthalenedicarboximidoyl);

*N-(1,8-naphthalenedicarboximidoyl);

*N-indoloyl;

*N-(2-pyrrolodinonyl);

*N-succinimidoyl;

*N-maleimidoyl;

*3-hydantoinyl;

*1,2,4-urazolyl;

*amido;

*urethane;

*urea;

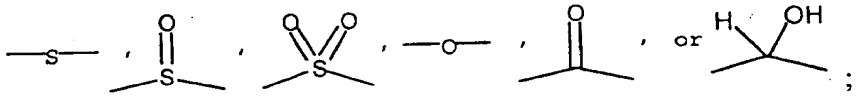
*nonaromatic substituted or unsubstituted heterocycles containing and connected through a N atom, and comprising one or two additional N, O, S, SO, or $SO_2$, and containing zero, one or two carbonyls, and optionally bearing a fused benzene or pyridine ring;

*amino;

*corresponding heteroaryl moieties in which the aryl portion of an aryl-containing $R^7$ group comprises 4 - 9 carbons and at least one N, O, or S heteroatom;

*$-(CH_2)_vZR^8$ in which v is 0 or an integer of 1 - 4, wherein

Z represents




;

and

$R^8$ is selected from the group consisting of:

*alkyl;

*aryl;

*heteroaryl;

*arylalkyl;

*heteroaryl-alkyl; and

*-C(O)$R^9$ in which $R^9$ represents alkyl of at least two carbons, aryl, heteroaryl, arylalkyl, or heteroaryl-alkyl;

and with the further provisos that

- when $R^8$ is -C(O)$R^9$ , Z is S or O;
- when Z is O, $R^8$ may also be alkyleneoxy or polyalkyleneoxy terminated with H, alkyl, or phenyl; and

*trialkylsilyl-substituted alkyl.

Furthermore, aryl or heteroaryl portions of any of the T or $R^6$ groups optionally may bear up to two substituents selected from the group consisting of -$(CH_2)_yC(R^4)(R^3)OH$, -$(CH_2)_yOR^4$, -$(CH_2)_ySR^4$, -$(CH_2)_yS(O)R^4$, -$(CH_2)_yS(O)_2R^4$, -$(CH_2)_ySO_2N(R^4)_2$, -$(CH_2)_yN(R^4)_2$, -$(CH_2)_yN(R^4)COR^{12}$, -$OC(R^4)_2O$- in which both oxygen atoms are connected to the aryl ring, $(CH_2)_yCOR^4$, -$(CH_2)_yCON(R^4)_2$, -$(CH_2)_yCO_2R^4$, -$(CH_2)_yOCOR^4$, -halogen, -CHO, -$CF_3$, -$NO_2$, -CN, and -$R^3$, in which y is 0 - 4. $R^3$ and $R^4$ are defined as above; in addition, any two $R^4$ which are attached to one nitrogen may be joined to form a heterocycle such as morpholine, thiomorpholine, pyrrolidine, or a piperidine ring.

Pharmaceutically acceptable salts of these compounds as well as commonly used prodrugs of these compounds such as O-acyl derivatives of invention compounds which contain hydroxy groups are also within the scope of the invention.

In most related reference compounds of the prior art, the biphenyl portion of the molecule is unsubstituted, and the propanoic or butanoic acid portion is either unsubstituted or has a single methyl or phenyl group. Presence of the larger phenyl group has been reported to cause prior art compounds to be inactive as anti-inflammatory

analgesic agents. See, for example, R.G. Child, et al., J. Pharm. Sci., 66, 466-476 (1977). By contrast, it has now been found that compounds which exhibit potent MMP inhibitory activity contain a substituent of significant size on the propanoic or butanoic portion of the molecule. The biphenyl portions of the best MMP inhibitors also preferably contain a substituent on the 4' position, although when the propanoic or butanoic portions are optimally substituted, the unsubstituted biphenyl compounds of the invention have sufficient activity to be considered realistic drug candidates.

In addition to the above-described compounds, the invention also relates to pharmaceutical compositions having matrix metalloprotease inhibitory activity, which compositions comprise a compound of the invention as described above and in more detail in the detailed description below, and a pharmaceutically acceptable carrier.

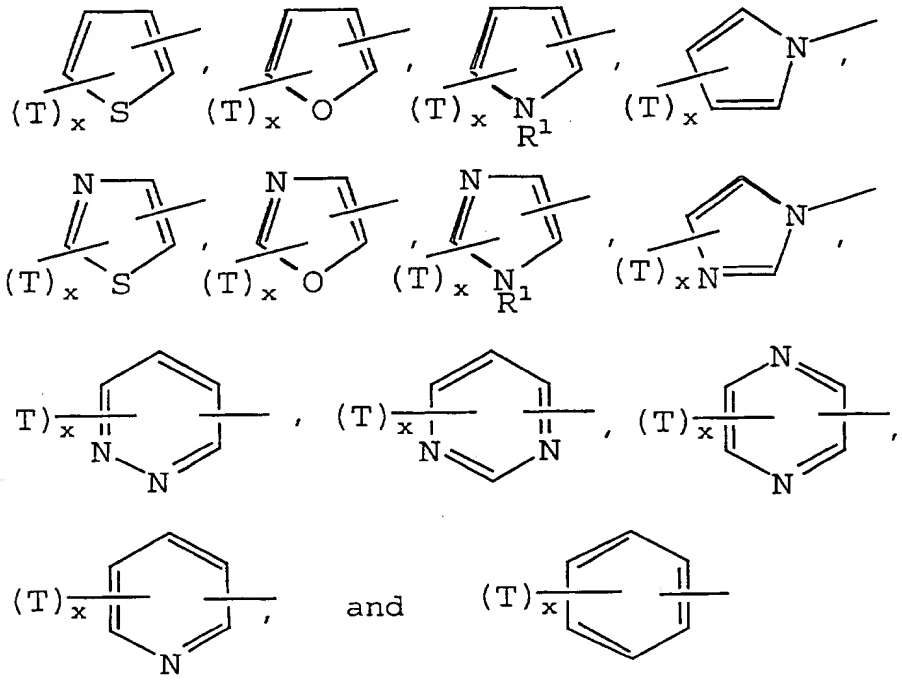
The invention also relates to a method of treating a mammal such as a human, a farm animal, or a domestic pet, to achieve an effect, in which the effect is: treatment and prevention of acute and chronic neurodegenerative disorders including stroke, spinal cord and traumatic brain injury, amyotrophic lateral sclerosis, cerebral amyloid angiopathy, CNS injuries in AIDS, Parkinson's disease, Alzheimer's disease, Huntington's diseases, prion diseases, myasthenia gravis, Duchenne's muscular dystrophy; diseases linked to $TNF_{\alpha}$ production including myelodysplastic syndromes, acute encephalitis; pain; neuropathies including drug induced neuropathy, mechanical damage neuropathy; intoxications including drug induced intoxication, alcohol induced intoxication; migraine; aneurysmal diseases including those of the brain; brain edemas as a result of pre-operative treatment for brain and spinal surgery including cerebral blood vessel surgery, removal of surface tumors; pre-operative treatment during cardiac by-pass surgery; depression; schizophrenia; anxiety the method comprising administering an amount of a compound of the invention as described above, and in more detail in the detailed description below, which is effective to inhibit the activity of at least one matrix metalloprotease, resulting in achievement of the desired effect.

**Detailed Description**

More particularly preferred are for the use for the prevention and treatment of cerebral diseases are compounds having matrix metalloprotease inhibitory activity of the generalized formula:

$$(T)_XA\text{-}B\text{-}D\text{-}E\text{-}CO_2H \qquad (I)$$

in which $(T)_XA$ represents a substituted or unsubstituted aromatic or heteroaromatic moiety selected from the group consisting of:



in which $R^1$ represents H or alkyl of 1 - 3 carbons.

In these structures, the aromatic ring is referred to as the A ring or A unit, and each T represents a substituent group, referred to as a T group or T unit. Substituent groups T are independently selected from the group consisting of: the halogens -F, -Cl, -Br, and -I; alkyl of 1 - 10 carbons; haloalkyl of 1 - 10 carbons; haloalkoxy of 1 - 10 carbons; alkenyl of 2 - 10 carbons; alkynyl of 2 - 10 carbons; $-(CH_2)_pQ$ in which p is

0 or an integer 1 - 4; -alkenyl-Q in which the alkenyl moiety comprises 2 - 4 carbons; and -alkynyl-Q in which the alkenyl moiety comprises 2 - 7 carbons. Q in each of the latter three groups is selected from the group consisting of aryl of 6 - 10 carbons; heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom; -CN; -CHO; $-NO_2$; $-CO_2R^2$; $-OCOR^2$; $-SOR^3$; $-SO_2R^3$; $-CON(R^4)_2$ ; $-SO_2N(R^4)_2$ ; $-C(O)R^2$ ; $-N(R^4)_2$; $-N(R^2)COR^2$; $-N(R^2)CO_2R^3$; $-N(R^2)CON(R^4)_2$; $-CHN_4$; $-OR^4$; and $-SR^4$. The groups $R^2$, $R^3$, and $R^4$ are defined as follows.

$R^2$ represents H; alkyl of 1 - 6 carbons; aryl of 6 - 10 carbons; heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom; arylalkyl in which the aryl portion contains 6 - 10 carbons and the alkyl portion contains 1 - 4 carbons; or heteroaryl-alkyl in which the heteroaryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkyl portion contains 1 - 4 carbons.

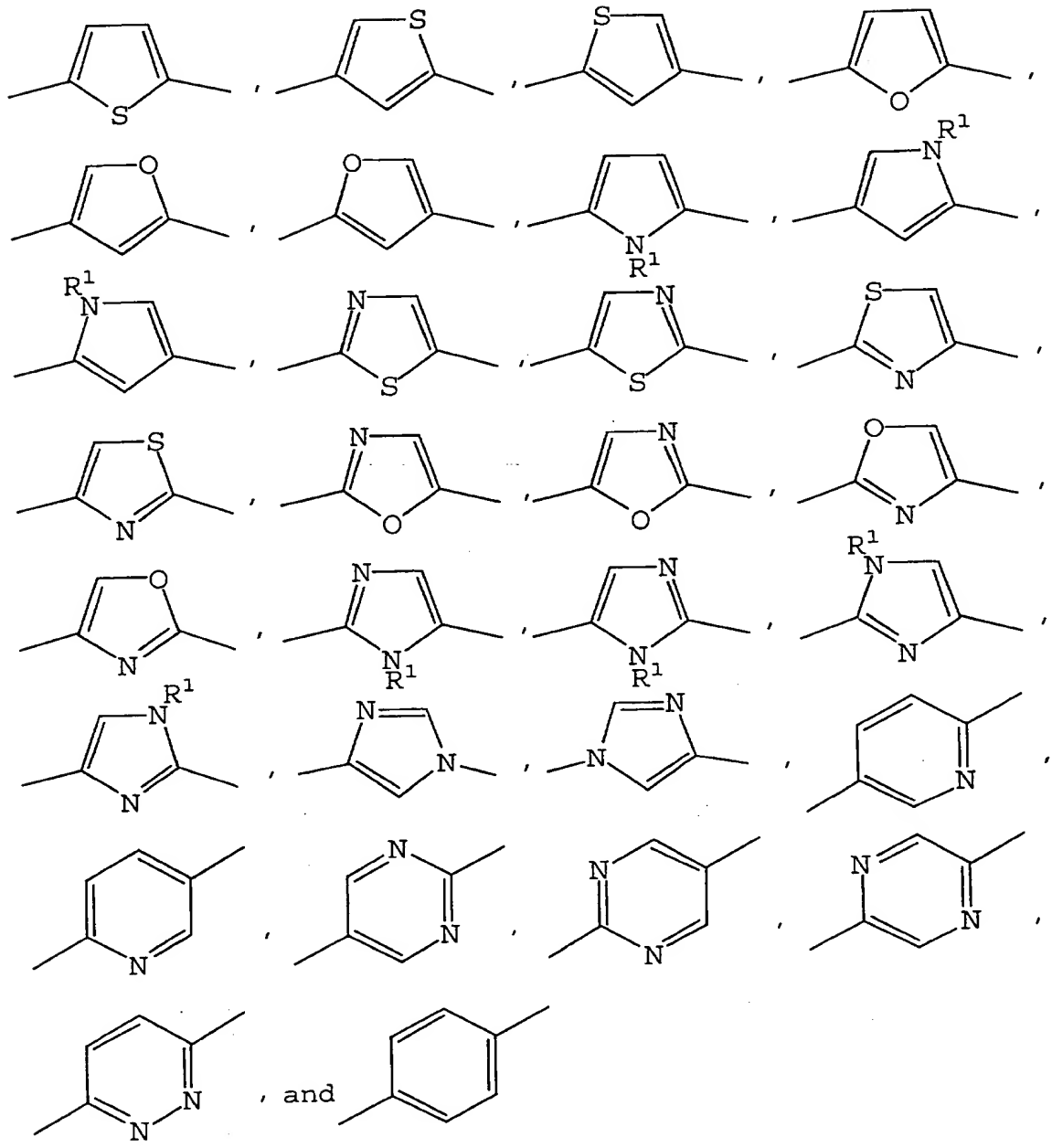
$R^3$ represents alkyl of 1 - 4 carbons; aryl of 6 - 10 carbons; heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom; arylalkyl in which the aryl portion contains 6 - 10 carbons and the alkyl portion contains 1 - 4 carbons; or heteroaryl-alkyl in which the heteroaryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkyl portion contains 1 - 4 carbons.

$R^4$ represents H; alkyl of 1 - 12 carbons; aryl of 6 - 10 carbons; heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom; arylalkyl in which the aryl portion contains 6 - 10 carbons and the alkyl portion contains 1 - 4 carbons; heteroaryl-alkyl in which the heteroaryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkyl portion contains 1 - 4 carbons; alkenyl of 2 - 12 carbons; alkynyl of 2 - 12 carbons; $-(C_qH_{2q}O)_rR^5$ in which q is 1-3, r is 1 - 3, and $R^5$ is H provided q is greater than 1, or $R^5$ is alkyl of 1 - 4 carbons, or phenyl; alkylenethio terminated with H, alkyl of 1-4 carbons, or phenyl; alkyleneamino terminated with H, alkyl of 1-4 carbons, or phenyl; $-(CH_2)_sX$ in which s is 1-3 and X is halogen; $-C(O)OR^2$; or $-C(O)R^2$.

When two $R^4$ groups are situated on a nitrogen, they may be joined by a bond to form a heterocycle, such as, for example, a morpholine, thiomorpholine, pyrrolidine, or piperidine ring.

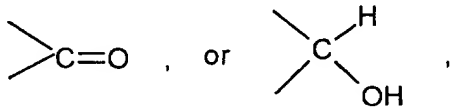
Any unsaturation in a moiety which is attached to Q or which is part of Q is separated from any N, O, or S of Q by at least one carbon atom, and the number of substituents, designated x, is 0, 1, or 2.

In the generalized formula (I), B represents a bond or an optionally substituted aromatic or heteroaromatic ring selected from the group consisting of:



in which $R^1$ is defined as above and each $R^1$ may be the same or different. These rings are referred to as the B ring or B unit. There may be 0-2 substituents T on the B ring, T being defined as above.

In the generalized formula (I), D represents the moieties



In the generalized formula (I), E represents a chain of n carbon atoms bearing m substituents $R^6$, referred to as $R^6$ groups or $R^6$ units. The $R^6$ groups are independent substituents, or constitute spiro or nonspiro rings. Rings may be formed in two ways: a) two groups $R^6$ are joined, and taken together with the chain atom(s) to which the two R6 group(s) are attached, and any intervening chain atoms, constitute a 3 - 7 membered ring, or b) one group $R^6$ is joined to the chain on which this one group $R^6$ resides, and taken together with the chain atom(s) to which the $R^6$ group is attached, and any intervening chain atoms, constitutes a 3 - 7 membered ring. The number n of carbon atoms in the chain is 2 or 3, and the number m of $R^6$ substituents is an integer of 1 - 3.

Each group $R^6$ is independently selected from the group consisting of the substituents listed below as items 1) - 16).

1) fluorine;

2) hydroxyl, with the proviso that a single carbon atom may bear no more than one hydroxyl group;

3) alkyl of 1 - 10 carbons;

4) aryl of 6 - 10 carbons;

5) heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom;

6) arylalkyl in which the aryl portion contains 6 - 10 carbons and the alkyl portion contains 1 - 8 carbons;